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TRANSMITTAL LETTER (General - Patent Pending)	Docket No. 49477

OIPE APR 05 2000 PATENT & TRADEMARK OFFICE

In Re Application Of: **J. Van Groeninghen**

Serial No.	Filing Date	Examiner	Group Art Unit
09446,996	**December 30, 1999**		

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Title: **METHOD FOR RECOGNIZING AND DETERMINING GNRH RECEPTORS AND THE USE OF GNRH AGONISTS AND OTHER GNRH RECEPTOR LIGANDS FOR THE TREATMENT WITH GNRH RECEPTORS OF TUMORS ORIGINATING IN THE BRAIN AND/OR NERVOUS SYSTEM AND/OR MENINGES AND/OR KAPOSI**

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

Transmitted herewith is:

English Translation of the International Preliminary Examination Report submitted on December 30, 1999

in the above identified application.

- ☒ No additional fee is required.
- ☐ A check in the amount of is attached.
- ☒ The Assistant Commissioner is hereby authorized to charge and credit Deposit Account No. **04-1105** as described below. A duplicate copy of this sheet is enclosed.
  - ☐ Charge the amount of
  - ☐ Credit any overpayment.
  - ☒ Charge any additional fee required.

Christine C. O'Day

Signature

Dated: 30 March 2000

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I certify that this document and fee is being deposited on 3/30/00 with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

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Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 159-1 PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DE98/01902	International filing date (*day/month/year*) 03 July 1998 (03.07.1998)	Priority date (*day/month/year*) 04 July 1997 (04.07.1997)
International Patent Classification (IPC) or national classification and IPC G01N 33/3		
Applicant VAN GROENINGHEN, Johannes, Christianus		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02 February 1999 (02.02.1999)	30 September 1999 (30.09.1999)
Name and mailing address of the IPEA/EP European Patent Office D-80298 Munich, Germany Facsimile No. 49-89-2399-4465	Authorized officer Telephone No. 49-89-2399-0

International application No.
PCT/DE98/01902

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-27, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-13, filed with the letter of 06 September 1999 (06.09.1999),
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/3-3/3, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 10, 11, 13

because:

☒ the said international application, or the said claims Nos. 10, 11, 13 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See Supplemental Box

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

Claims 10, 11 and 13 refer to a subject matter which, in the opinion of this authority, falls under PCT Rule 67.1(iv). For this reason, a report has not been produced on the industrial applicability of the subject matter of these claims (PCT Article 34(4)(a)(i)).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	4-6, 10-13	YES
	Claims	1-3, 7-9	NO
Inventive step (IS)	Claims		YES
	Claims	1-13	NO
Industrial applicability (IA)	Claims	1-9, 12	YES
	Claims		NO

2. Citations and explanations

The following documents are referred to:

D1: Chemical Abstracts, Mol. Androl., Vol. 8, 1996, pages 95-125

D2: Abstract, Medline, Synapse, Vol. 1, 1987, pages 567-71

D3: Abstract, Medline, Mol. Cell Endocrinol., Vol. 114, 1995, pages 51-56

D4: Abstract BIOSIS, J. Clin. Invest., Vol. 93, 1994, pages 2332-2339

D5: WO-A-9009799

D6: Biological Signals, Vol. 5, 1996, pages 63-69

D7: Abstract, Medline, Cancer Lett., Vol. 81, 1994, pages 177-184

Documents D2, D3, D6 and D7 are not indicated in the international search report. Copies of these documents have already been sent to the applicants.

1. Claim 1 refers to a method for recognising and determining GnRH receptors on tumour cells originating in the brain and/or nervous system and/or the meninges and/or Kaposi's sarcoma, which involves contacting said cells with a ligand for a

GnRH receptor and determining whether a bond has taken place.

1.1 Abstract BIOSIS, J. Clin. Invest., Vol. 93, 1994, pages 2332-2339 (D4) describes determining and characterising GnRH receptors on benign tumour cells of the pituitary by means of the GnRH antagonist "Antide" (see abstract). D4 thus describes a method which contains all of the technical features necessary for achieving the purpose of Claim 1 without them needing to be modified. Moreover, it describes a medical use of this method. D4 is therefore considered prejudicial to the novelty of the subject matter of Claims 1 and 7 to 9, such that it does not meet the requirements of PCT Article 33(2).

D2 describes the characterisation and localisation of GnRH receptors in the CNS tissue of rats by means of a radioligand assay (see abstract). In the same way as document D4, it thus describes a method which contains all of the technical features necessary for achieving the purpose of Claim 1 without them needing to be modified. It is therefore considered prejudicial to the novelty of the subject matter of Claims 1, 3 and 7 to 9, such that it does not meet the requirements of PCT Article 33(2).

D3 discloses fluoresent-marked anti-GnRH receptor antibodies for detecting GnRH receptors on pituitary and tumour cells (see abstract). Since the antibody is specifically bonded to the GnRH receptor and is therefore used in the sense of a "ligand" as per Claim 1 and additionally has a medical use, D3 is, for the same reasons as D2 and D4, considered

prejudicial to the novelty of the subject matter of Claims 1 to 3 and 7 to 9, such that it does not meet the requirements of PCT Article 33(2).

The subject matter of Claims 1 to 3 and 7 to 9 is consequently not novel and therefore does not meet the requirements of PCT Article 33(2).

1.2 In contrast, the subject matter of Claims 4 to 6 and 10 to 13 is not known from any of the available prior art documents and is consequently considered novel. The subject matter of these claims therefore meets the requirements of PCT Article 33(2).

2. However, the subject matter of Claims 4 to 6 and 10 to 13 does not appear to involve an inventive step.

D1 describes the tissue distribution and the regulation of the gene expression of the GnRH receptor in various cells in the central nervous system (CNS) and various tumour cells in different organisms (see abstract).

D5 describes conjugates of GnRH agonists and antagonists with toxins and their use for destroying cells of the frontal pituitary gland or for treating sicknesses dependent on gonadotropin (see abstract and page 18, line 17 and Fig. 5).

D6 discloses the presence of GnRH receptors mRNA in different types of tissue, and tumour cells derived therefrom. Brain tissue is explicitly mentioned (see abstract, page 66, left-hand column, first paragraph).

D7 describes the cytotoxic effect of an anti-GnRH receptor polyclonal antibody serum on an ovarian cancer cell line and its use in the therapeutic treatment of ovarian and uterine neoplasias (see abstract).

The closest prior art is represented by D4. This document already discloses the bonding of a GnRH antagonist to the GnRH receptor of a pituitary tumour. The subject matter of Claim 4 differs therefrom in the use of a marked anti-ligand, preferably an antibody, to detect GnRH receptors on tumour cells which are derived from brain or other CNS tissues. This distinction results in GnRH receptor identification by means of an immunological identification method. The fact that the prior art and the subject matter of Claim 4 differ additionally in that different tumour cell types are identified is not relevant for the analysis of inventive step, since here only the method *per se* is considered (see also point 1.1 above).

The object of the present invention was consequently to find an alternative method of identifying GnRH receptors.
IFA tests, however, constitute generally known alternative methods of identification. Their use can therefore not be acknowledged as evidence of the presence of inventive step.

The subject matter of Claims 5 and 6 describes a standard method and different tumour cell lines, which do not, however, contain any feature which, in combination with the subject matter of Claim 1, would make this appear inventive over the cited

prior art.

The subject matter of Claims 10 and 11 refers to a second medical use of GnRH agonists and antagonists in the treatment of a tumour originating in the brain and/or the nervous system and/or the meninges and/or the treatment of a Kaposi's sarcoma.

D6 is considered the closest prior art. This document discloses the presence of the GnRH receptor mRNA in different types of tissue, and tumour cells derived therefrom. Brain tissue is explicitly mentioned (see abstract). In addition, it is mentioned that GnRH receptors were found in the most varied tumour cell types, *inter alia*, in pituitary tumour cells as well, and that GnRH analogues can prevent the proliferation of these cells *in vitro* (see page 66, left-hand column, first paragraph). The subject matter of Claims 10 and 11 differs therefrom in that the aforementioned GnRH analogues are used to treat tumour cells which can be derived from the brain, CNS and meninges. This means that a known therapeutic approach is used to treat further brain tumours.

The object of the present invention was consequently to develop an approach for treating tumours in the brain, CNS and meninges.

However, it is known from the prior art that, as well as the pituitary, further cell types of the brain or the CNS express GnRH receptors and present them on their surface (see D1 and D2). For this reason, it was obvious for a person skilled in the art to combine the subject matter of D6 with D1 or

D2 so as to achieve the aforementioned object. The subject matter of Claims 12 and 13 is obvious from D5, since conjugates of GnRH agonists and antagonists with toxins, and the use of same to destroy pituitary cells, are already mentioned therein (see abstract and page 18, line 17 and Fig. 5). Furthermore, anti-GnRH receptor antibodies have a growth-inhibiting or cytotoxic effect in cells of the endometrium and an ovarian cancer cell line (OVCAR-3), whose growth is dependent on GnRH (D7).

The subject matter of Claims 4 to 6 and 10 to 13 does not therefore involve an inventive step and does not therefore meet the requirements of PCT Article 33(3).

3. The PCT contracting states do not have uniform criteria for assessing the industrial applicability of the subjects of Claims 10, 11 and 13 in their current form. Patentability can also depend on the wording of the claims. The EPO, for example, does not recognise industrial applicability of claims to the use of a compound in a medical treatment; it does, however, allow claims to the first use of a known compound in a medical treatment or to the use of such a compound in the manufacture of a drug for a new medical treatment.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Contrary to the requirements of PCT Rule 5.1(a)(ii), the description does not indicate the relevant prior art disclosed in document D2, or cite that document itself.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Although Claims 10 and 11 were written as separate, independent claims, they appear in fact to refer to one and the same subject matter and differ clearly from one another only in mutually diverging definitions of the subject matter for which protection is sought. The claims are consequently not concise. Furthermore, the claims as a whole lack clarity, since, due to the large number of independent claims, it is difficult, if not impossible, to determine the subject matter for which protection is sought, and thus identifying the scope of protection is made unacceptably difficult for third parties.

   For this reason, Claims 10 and 11 do not meet the requirements of PCT Article 6.

2. The term "Kaposi's sarcoma" in Claim 6 is already used in the preamble of Claim 1. This overlap in the scope of protection leads to a lack of clarity, in contravention of the requirements of PCT Article 6. The same applies to the subject matter of Claims 10 and 11, since here too the term "Kaposi's sarcoma" appears in both claims.

3. Furthermore, the subject matter of Claim 9 is unclear, since it uses different categories of claim (PCT Article 6).